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(54) Title: PHARMACEUTICAL SALTS

(54) Bezeichnung: PHARMAZEUTISCHE SALZE

(57) Abstract: The invention relates to pharmaceutical salts comprised of a pharmaceutical active substance and of at least one sugar substitute, to medicaments containing these salts, and to the use of these salts for producing medicaments.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft pharmazeutische Salze aus einem pharmazeutischen Wirkstoff und wenigstens einem Zuckerersatzstoff, Arzneimittel enthaltend diese Salze sowie die Verwendung dieser Salze zur Herstellung von Arzneimitteln.

**Pharmaceutical salts**

The present invention relates to pharmaceutical salts of an active compound and at least one sugar substitute, medicaments comprising these salts, and the  
5 use of these salts for the production of medicaments.

On oral administration, a large number of pharmaceutical active compounds having excellent  
10 activity lead to a strongly bitter, often nauseating taste sensation in the patient. In some patients, lack of adherence to the dosage instructions and a lack of acceptance of the corresponding medicaments which release such an active compound as early as during  
15 taking result from this negative taste experience.

The formulation of pharmaceutical active compounds having very good water solubility to give medicaments frequently causes problems in pharmaceutical practice.  
20 Thus the preparation of pharmaceutical forms having controlled release is often made difficult on account of the very good water solubility of active compound salts. A delaying of the release of these active compounds can in fact be achieved, for example, by  
25 coating the pharmaceutical forms with release-delaying film coatings. This manner of delaying the release, however, is associated with a relatively high outlay, since release-delaying film coatings from aqueous coating systems are frequently only an inadequate  
30 diffusion barrier for active compounds having very good water solubility. The preparation of these delayed-release active compound preparations therefore requires relatively complicated coating processes with multilayer films. If such release-delaying coatings are  
35 applied from organic solvents, the environmental and solvent residue problems associated therewith additionally make the preparation of appropriate preparations more expensive.

**CONFIRMATION COPY**

It was therefore the object of the present invention to make available pharmaceutical combinations of active compounds which have no bitter taste. Preferably, the  
5 corresponding active compounds should be simpler to formulate and their release should be more effectively delayed.

According to the invention, this object is achieved by  
10 the provision of pharmaceutical salts, i.e. physiologically tolerable salts, from a pharmaceutical active compound and at least one sugar substitute.

The present invention therefore relates to  
15 pharmaceutical salts of a pharmaceutical active compound and at least one sugar substitute, the respective pharmaceutical salts of a sugar substitute and tramadol, (+)-tramadol, (-)-tramadol, (+)-demethyltramadol and (-)-demethyltramadol being excepted.

20 In a preferred embodiment of the present invention, the solubility of the pharmaceutical salts according to the invention in water is  $\leq 250$  mg/ml of water, preferably  $\leq 200$  mg/ml, particularly preferably  $\leq 150$  mg/ml, very  
25 particularly preferably  $\leq 100$  mg/ml. This can also be seen in particular in the fact that the water solubility of the pharmaceutical salts according to the invention compared with the water solubility of the best water-soluble salt of the corresponding active  
30 compound according to Pharmazeutische Stoffliste [Pharmaceutical Substance List], 12th edition ABDA Pharma-Daten-Service, 65735 Eschborn/Taunus, is preferably lowered by at least 50%, preferably by at least 65%, particularly preferably by at least 75%,  
35 very particularly preferably by at least 85%, compared with the corresponding hydrochloride. The corresponding literature description is hereby inserted as a reference and is thus regarded as part of the disclosure.

According to the invention, suitable sugar substitutes are all sugar substitutes which can form a salt with the respective pharmaceutical active compound with formation of an at least singly negatively charged form. According to the invention, pharmaceutical salts are also included in which the pharmaceutical active compound has two or more different sugar substitutes as salt components. Preferably, the pharmaceutical salts according to the invention contain saccharin, cyclamate or acesulfam, particularly preferably saccharin, as salt-forming sugar substitutes.

According to the invention, suitable active compounds are all pharmaceutical active compounds which can form a salt in anionic form with the respective sugar substitute(s) with formation of an at least singly positively charged form.

In a further preferred embodiment of the present invention, the salt-forming active compound in the pharmaceutical salt according to the invention is selected from the group consisting of the salt-forming analgesics, antiobesity agents, analeptics, anti-hypoxemics, antirheumatics, opioid antagonists, anthelmintics, antiallergics, antiarrhythmics, antibiotics, antidementives (nootropics), antidiabetics, antiemetics, antivertiginous agents, antiepileptics, antihypertensives, antihypotensives, antimycotics, antiinflammatories, antitussives, expectorants, arteriosclerosis agents,  $\beta$ -receptor blockers, calcium channel blockers, broncholytics, antiasthmatics, cholinergics, diuretics, circulation-promoting agents, weaning agents, geriatrics, hypnotics, sedatives, immunomodulators, oral therapeutics, pharyngeal therapeutics, coronary agents, hypolipidemics, local anesthetics, neural therapeutics, gastric agents, intestinal agents, migraine agents, muscle relaxants, anesthetics, neuropathy preparations, ophthalmo-

logicals, otologicals, Parkinson agents, psychopharmaceuticals, rhinologicals, sinusitis agents, spasmolytics, platelet aggregation inhibitors, tuberculosis agents, urologicals and cytostatics.

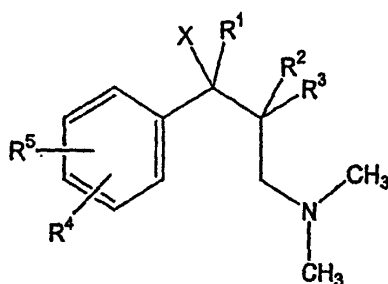
- 5 Particularly preferably, the salt-forming active compound is selected from the group consisting of the salt-forming analgesics, analeptics, antihypoxemics, antiallergics, antiarrhythmics, antiemetics, anti-vertiginous agents, antihypertensives, anti-  
10 hypotensives, antitussives, expectorants,  $\beta$ -receptor blockers, calcium channel blockers, ophthalmologicals, otologicals, spasmolytics and urologicals. Very particularly preferably, the salt-forming active compound is selected from the group consisting of the  
15 salt-forming analgesics, tramadol, (+)-tramadol, (-)-tramadol, (+)-demethyltramadol and (-)-demethyltramadol being excepted.

- If the pharmaceutical active compound is a salt-forming  
20 analgesic, it is preferably a salt-forming opioid or a salt-forming opioid analog, such as disclosed in E. Friderichs, T. Christoph, H. Buschmann, "Analgesics and Antipyretics"; Ullmann's Encyclopedia of Industrial Chemistry, Sixth Edition on CD-ROM, Wiley-VCH,  
25 Weinheim, 2000 or in Pharmaceuticals, J.L. McGuire (Editor), Analgesics and Antipyretics, Volume 2, pages 341-434, Wiley-VCH, Weinheim or ephedrine, chloroquine, lidocaine, ethaverine, preglumetacin or triflu-  
promazine. The corresponding disclosures are hereby  
30 inserted as a reference and are thus regarded as part of the present disclosure. Particularly preferably, the salt-forming analgesic is selected from the group consisting of morphine, codeine, ethylmorphine, diacetylmorphine, dihydrocodeine, etorphine,  
35 hydrocodone, hydromorphone, levorphanol, oxycodone, oxymorphone, pethidine, ketobemidone, fentanyl, alfentanil, remifentanil, sufentanil, levomethadone, levomethadyl, dextro-moramide, dextropropoxyphene, diphenoxylate, piri-tramide, tilidine, buprenorphine,

butorphanol, dezozine, meptazinol, nalbuphine, nalorphine, pentazo-cine, flupirtin and nefopam or a representative of the group consisting of ephedrine, chloroquine, lidocaine, ethaverine, preglumetacin and triflupromazine. Very particularly preferably, the salt-forming analgesic is a salt-forming opioid or opioid analog selected from the group consisting of morphine, codeine, hydrocodone, hydromorphone, oxycodone, tilidine, fentanyl and buprenorphine.

10

Likewise preferably, the salt-forming active compound is a salt-forming compound of 1-phenyl-3-dimethylamino-propane compounds of the general formula I



15

in which in each case

X is OH, F, Cl, H or an OCOR<sup>6</sup> group,

20

R<sup>1</sup> is a C<sub>1-4</sub>-alkyl group,

R<sup>2</sup> is H or a C<sub>1-4</sub>-alkyl group and R<sup>3</sup> is H or a straight-chain C<sub>1-4</sub>-alkyl group or the radicals R<sup>2</sup> and R<sup>3</sup> together form a C<sub>4-7</sub>-cycloalkyl radical, and

25

if R<sup>5</sup> is H, R<sup>4</sup> is meta-O-Z where Z is H, C<sub>1-3</sub>-alkyl, PO(O-C<sub>1-4</sub>-alkyl)<sub>2</sub>, CO(OC<sub>1-5</sub>-alkyl), CONH-C<sub>6</sub>H<sub>4</sub>-(C<sub>1-3</sub>-alkyl), CO-C<sub>6</sub>H<sub>4</sub>-R<sup>7</sup>, where R<sup>7</sup> is ortho-OCOC<sub>1-3</sub>-alkyl or meta- or para-CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub> where R<sup>8</sup> is C<sub>1-4</sub>-alkyl or 4-morpholino, or R<sup>4</sup> is meta-S-C<sub>1-3</sub>-alkyl, meta-Cl, meta-F, meta-CR<sup>9</sup>R<sup>10</sup>R<sup>11</sup> where R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> are H or F, ortho-OH, ortho-O-C<sub>2-3</sub>-

30

alkyl, para-F or para-CR<sup>9</sup>R<sup>10</sup>R<sup>11</sup> where R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> are H or F, or if R<sup>5</sup> is para-Cl, -F, -OH or -O-C<sub>1-3</sub>-alkyl, R<sup>4</sup> is meta-Cl, -F, -OH or -O-C<sub>1-3</sub>-alkyl, or R<sup>4</sup> and R<sup>5</sup> together are 3,4-OCH=CH- or 3,4-OCH=CHO-,

5

R<sup>6</sup> is C<sub>1-3</sub>-alkyl,

in the form of their possible stereoisomers as racemates or diastereomerically pure enantiomers or in the form of mixtures of enantiomers, in which the respective enantiomers are present in nonequimolar amounts.

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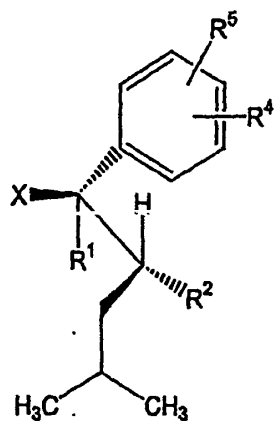
Preferred is a salt-forming compound of 1-phenyl-3-dimethylaminopropane compounds of the general formula I in which X is OH, F, Cl or H, R<sup>1</sup> is a C<sub>1-4</sub>-alkyl group, R<sup>2</sup> is H or CH<sub>3</sub> and R<sup>3</sup> is H or CH<sub>3</sub> and if R<sup>5</sup> is H, R<sup>4</sup> is meta-O-C<sub>1-3</sub>-alkyl, meta-OH, meta-S-C<sub>1-3</sub>-alkyl, meta-F, meta-Cl, meta-CH<sub>3</sub>, meta-CF<sub>2</sub>H, meta-CF<sub>3</sub> or para-CF<sub>3</sub> or if R<sup>5</sup> is a para-Cl or -F, R<sup>4</sup> is meta-Cl or -F, or R<sup>4</sup> and R<sup>5</sup> together are 3,4-OCH=CH-.

15

20

Particularly preferred is a salt-forming compound of 1-phenyl-3-dimethylaminopropane compounds of the general formula I in which the radicals R<sup>2</sup> and R<sup>3</sup> have different meanings and which are present in the form of their diastereomers having the configuration Ia

25



Ia

Very particularly preferred is a salt-forming compound  
of 1-phenyl-3-dimethylaminopropane compounds of the  
5 general formula I, selected from the group consisting  
of

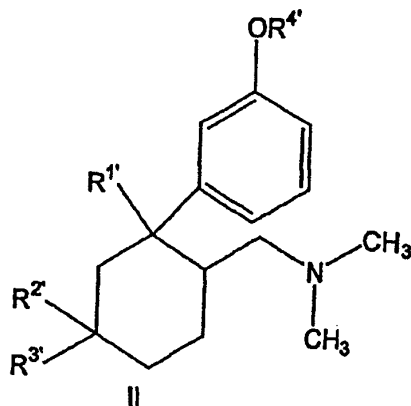
- (1RS,2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-  
propyl)phenol,
- 10 (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-  
phenol,
- (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-  
15 phenol,
- (2RS,3RS)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-  
pentan-3-ol,
- 20 (-)-(1S,2S)-3-(3-dimethylamino-1-ethyl-1-fluoro-  
2-methylpropyl)phenol,
- (+)-(1R,2R)-3-(3-dimethylamino-1-hydroxy-1,2-dimethyl-  
propyl)phenol,
- 25 (+)-(2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-  
2-methylpentan-3-ol and



(-)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-  
2-methylpentan-3-ol.

5 The preparation of the salt-forming compounds of  
1-phenyl-3-dimethylaminopropane compounds of the  
general formula I and, if appropriate, the separation  
into the pure optical antipodes can be carried out  
according to customary methods known to the person  
skilled in the art. Preferably, the preparation and, if  
10 appropriate, the separation is carried out as described  
in DE-A-4426245 or EP 0 693 475 B1, which are hereby  
inserted as reference and are thus regarded as part of  
the disclosure.

15 In a further preferred embodiment of the present  
invention, the pharmaceutical salt according to the  
invention contains as a salt-forming active compound a  
salt-forming compound of 6-dimethylaminomethyl-  
1-phenylcyclohexane compounds of the general formula  
20 II,



in which in each case

25

$R^{1'}$  is H, OH, Cl or F, preferably H, OH or F,

$R^{2'}$  and  $R^{3'}$  are identical or different and are H,  $C_{1-4}$ -alkyl, benzyl,  $CF_3$ , OH,  $OCH_2-C_6H_5$ ,  $O-C_{1-4}$ -alkyl, Cl or F

with the proviso that at least one of the radicals  $R^{2'}$  or  $R^{3'}$  is H,

$R^{4'}$  is H,  $CH_3$ ,  $PO(O-C_{1-4}\text{-alkyl})_2$ ,  $CO(OC_{1-5}\text{-alkyl})$ ,  $CO-NH-C_6H_4-C_{1-3}\text{-alkyl}$ ,  $CO-C_6H_4-R^{5'}$ ,  $CO-C_{1-5}\text{-alkyl}$ ,  $CO-CHR^{6'}-NHR^{7'}$  or an unsubstituted or substituted pyridyl, thienyl, thiazoyl [sic] or phenyl group,

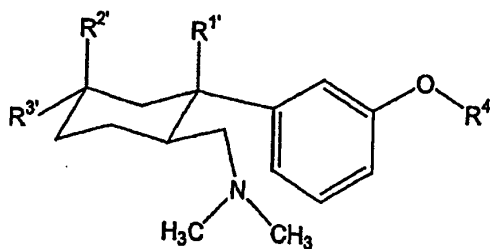
$R^{5'}$  is  $OC(O)C_{1-3}\text{-alkyl}$  in the ortho-position or  $CH_2-N(R^{8'})_2$  in the meta- or para-position, where  $R^{8'}$  is  $C_{1-4}\text{-alkyl}$  or both radicals  $R^{8'}$  together with N are the 4-morpholino radical, and

$R^{6'}$  and  $R^{7'}$  are identical or different and are H or  $C_{1-6}\text{-alkyl}$ ,

with the proviso that if both radicals  $R^{2'}$  and  $R^{3'}$  are H,  $R^{4'}$  is not  $CH_3$  if  $R^{1'}$  is H, OH or Cl or  $R^{4'}$  is not H if  $R^{1'}$  is OH,

in the form of their possible stereoisomers as racemates or diastereomerically pure enantiomers or in the form of mixtures of enantiomers, in which the respective enantiomers are present in nonequimolar amounts.

Preferred are salt-forming compounds of 6-dimethylaminomethyl-1-phenylcyclohexane compounds of the general formula II, which are present in the configuration as in the general formula IIa,



IIa

in which the phenyl ring and the dimethylaminomethyl group are in each case arranged in an equatorial position to one another.

- 5 Particularly preferred is a salt-forming compound of 6-dimethylaminomethyl-1-phenylcyclohexane compounds of the general formula II selected from the group consisting of
- 10 (-)-(1R,2R)-3-(2-dimethylaminomethylcyclohexyl)phenol,
- (1RS,3RS,6RS)-6-(dimethylaminomethyl)-1-(3-methoxyphenyl)cyclohexane-1,3-diol and
- 15 (1RS,3RS,6RS)-6-(dimethylaminomethyl)-1-(3-hydroxyphenyl)cyclohexane-1,3-diol.

The preparation of the salt-forming compounds of 6-dimethylaminomethyl-1-phenylcyclohexane compounds of

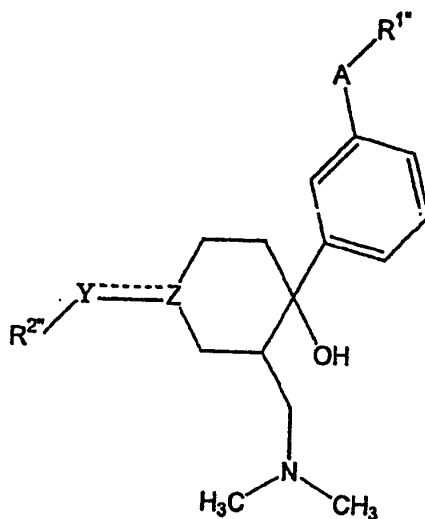
20 the general formula II and, if appropriate, the separation into the optically pure antipodes can be carried out according to customary methods known to the person skilled in the art. Preferably, the preparation and, if appropriate, the separation are carried out as

25 described in DE-A-19525137. The corresponding literature description is hereby inserted as reference and is thus regarded as part of the disclosure.

In a further preferred embodiment of the present

30 invention, the pharmaceutical salt according to the invention contains as a salt-forming active compound a salt-forming compound of 1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds of the general formula III,

35



III

in which in each case

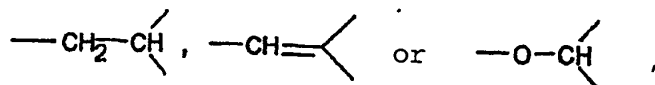
5 A is O or S,

R<sup>1''</sup> is H, C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>5-7</sub>-cycloalkyl or halogenated C<sub>1-6</sub>-alkyl,

the group  $\text{---Y=Z}$

10

is the group



15 R<sup>2''</sup> is C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, C<sub>5-7</sub>-cycloalkylmethyl, substituted or unsubstituted phenyl or substituted or unsubstituted benzyl,

20 in the form of their possible stereoisomers as racemates or diastereomerically pure enantiomers or in the form of mixtures of enantiomers, in which the

respective enantiomers are present in nonequimolar amounts.

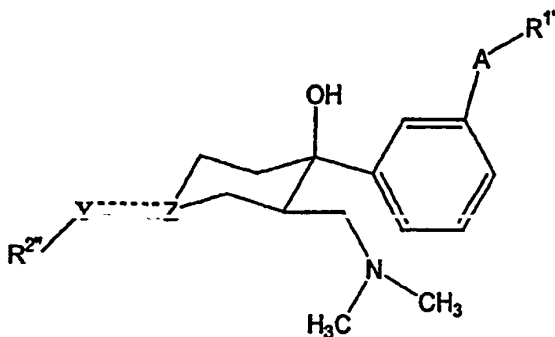
Preferred are salt-forming compounds of 1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds of the general formula III, in which  $R^{1''}$  is H,  $C_{1-4}$ -alkyl, 2'-methyl-2'-propenyl, cyclopentyl or fluoroethyl, with the proviso that  $R^{1''}$  is  $C_{1-4}$ -alkyl if A is S,

10  $R^{2''}$  is  $C_{1-4}$ -alkyl,  $C_{2-4}$ -alkenyl, cyclopentylmethyl, phenyl,  $C_{1-4}$ -alkoxyphenyl, benzyl,  $C_{1-4}$ -alkylbenzyl, mono- or dihalogenated phenyl or mono- or dihalogenated benzyl.

15 Particularly preferred are salt-forming compounds of 1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds of the general formula III, in which  $R^{1''}$  is H, methyl, ethyl, isopropyl, 2'-methyl-2'-propenyl, cyclopentyl or fluoroethyl, with the proviso that  $R^{1''}$  is methyl if A  
20 is S,

$R^{2''}$  is methyl, propyl, 2'-methylpropyl, allyl, 2'-methyl-2'-propenyl, cyclopentylmethyl, phenyl, 3-methoxyphenyl, benzyl, 4-tert-butylbenzyl, 4-chloro-  
25 benzyl, 4-fluorobenzyl or 3,4-dichlorobenzyl.

Very particularly preferred are salt-forming compounds of 1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds of the general formula III which are present  
30 in the configuration of the formula IIIa,



IIIa

in which the phenyl ring and the dimethylaminomethyl  
group are in each case arranged in an equatorial  
5 position to one another.

Most preferred is the salt-forming compound of  
1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds  
of the general formula III selected from the group  
10 consisting of

(+)-(1R,2R,4S)-2-(dimethylaminomethyl)-4-(4-fluoro-  
benzyloxy)-1-(3-methoxyphenyl)cyclohexanol,

15 (+)-(1R,2R,4S)-2-dimethylaminomethyl-4-(4-chloro-  
benzyloxy)-1-(3-methoxyphenyl)cyclohexanol and

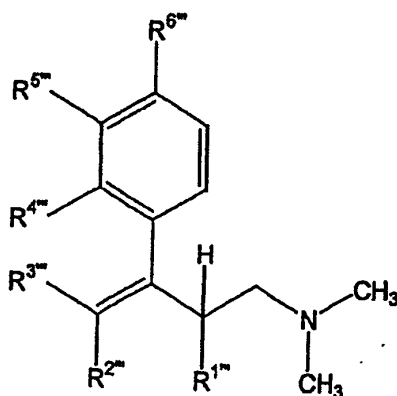
(+)-(1R,2R,4S)-3-[2-dimethylaminomethyl-4-(4-fluoro-  
benzyloxy)-1-hydroxycyclohexyl]phenol.

20

The preparation of the salt-forming compounds of  
1-phenyl-2-dimethylaminomethylcyclohexan-1-ol compounds  
of the general formula III and, if appropriate, the  
separation into the optically pure antipodes can be  
25 carried out according to customary methods known to the  
person skilled in the art. Preferably, the preparation  
and, if appropriate, the separation are carried out as  
described in DE-A-19547766, which is hereby inserted as

reference and is thus regarded as part of the disclosure.

In a further preferred embodiment of the present invention, the pharmaceutical salt contains as a salt-forming active compound a salt-forming compound of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV, in which [sic]



IV

the radical  $R^{1'''}$  is  $C_{1-5}$ -alkyl and  $R^{2'''}$  is H or  $C_{1-5}$ -alkyl or  $R^{1'''}$  and  $R^{2'''}$  together are  $-(CH_2)_{2-4}-$ ,  $-(CH_2)_2-CHR^{7'''}$  or  $-CH_2-CHR^{7'''}-CH_2-$ ,

$R^{3'''}$  is H or  $C_{1-5}$ -alkyl,

$R^{4'''}$  is H, OH,  $C_{1-4}$ -alkyl, O- $C_{1-4}$ -alkyl, O-benzyl,  $CF_3$ , O- $CF_3$ , Cl, F or  $OR^{8'''}$ ,

$R^{5'''}$  is H, OH,  $C_{1-4}$ -alkyl, O- $C_{1-4}$ -alkyl, O-benzyl,  $CHF_2$ ,  $CF_3$ , O- $CF_3$ , Cl, F or  $OR^{8'''}$  and

$R^{6'''}$  is H, OH,  $C_{1-4}$ -alkyl, O- $C_{1-4}$ -alkyl, O-benzyl,  $CF_3$ , O- $CF_3$ , Cl, F or  $OR^{8'''}$ ,

with the proviso that two of the radicals  $R^{4'''}$ ,  $R^{5'''}$  or  $R^{6'''}$  are H, or

$R^{4''''}$  and  $R^{5''''}$  together are  $-\text{CH}=\text{C}(\text{R}^{9''''})-\text{O}-$  or  $-\text{CH}=\text{C}(\text{R}^{9''''})-\text{S}-$ , with the proviso that  $\text{R}^{6''''}$  is H, or

$R^{5''''}$  and  $R^{6''''}$  together are  $-\text{CH}=\text{CH}-\text{C}(\text{OR}^{10''''})=\text{CH}-$ , with the  
5 proviso that  $R^{4''''}$  is H,

$R^{7''''}$  is  $\text{C}_{1-8}$ -alkyl,  $\text{C}_{3-8}$ -cycloalkyl,  $\text{O}-\text{C}_{1-4}$ -alkyl,  $\text{O}$ -benzyl,  $\text{CF}_3$ , Cl or F,

10  $R^{8''''}$  is  $\text{CO}-\text{C}_{1-5}$ -alkyl,  $\text{PO}(\text{O}-\text{C}_{1-4}$ -alkyl) $_2$ ,  $\text{CO}-\text{C}_6\text{H}_4-\text{R}^{11''''}$ ,  $\text{CO}(\text{O}-\text{C}_{1-5}$ -alkyl),  $\text{CO}-\text{CHR}^{12''''}-\text{NHR}^{13''''}$ ,  $\text{CO}-\text{NH}-\text{C}_6\text{H}_3-(\text{R}^{14''''})_2$  or an unsubstituted or substituted pyridyl, thienyl, thiazoyl [sic] or phenyl group,

15  $R^{9''''}$  is H or  $\text{C}_{1-4}$ -alkyl,

$R^{10''''}$  is H or  $\text{C}_{1-3}$ -alkyl,

$R^{11''''}$  is  $\text{OC}(\text{O})-\text{C}_{1-3}$ -alkyl in the ortho-position or  $\text{CH}_2-\text{N}-$   
20  $(\text{R}^{15''''})_2$  in the meta- or para-position, where  $\text{R}^{15''''}$  is  $\text{C}_{1-4}$ -alkyl or both radicals  $\text{R}^{15''''}$  together with N form the 4-morpholino radical,

$R^{12''''}$  and  $R^{13''''}$  are identical or different and are H,  
25  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{3-8}$ -cycloalkyl or  $R^{12''''}$  and  $R^{13''''}$  together are  $-(\text{CH}_2)_3-$ ,

$R^{14''''}$  is H, OH,  $\text{C}_{1-7}$ -alkyl,  $\text{O}-\text{C}_{1-7}$ -alkyl, phenyl,  $\text{O}$ -aryl,  $\text{CF}_3$ , Cl or F, with the proviso that the two radicals  
30  $R^{14''''}$  are identical or different,

in the form of their possible stereoisomers as racemates or diastereomerically pure enantiomers or in the form of mixtures of enantiomers, in which the  
35 respective enantiomers are present in nonequimolar amounts.



Preferred are salt-forming compounds of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV, in which

5  $R^{1''''}$  is  $C_{1-3}$ -alkyl and  $R^{2''''}$  is H or  $C_{1-3}$ -alkyl, or  $R^{1''''}$  and  $R^{2''''}$  together are  $-(CH_2)_{2-4}-$  or  $-(CH_2)_2-CHR^{7''''}$ ,  
 $R^{3''''}$  is H or  $C_{1-3}$ -alkyl,

10  $R^{4''''}$  is H, OH,  $CF_3$ , Cl, F or  $OR^{8''''}$ ,

$R^{5''''}$  is H, OH,  $C_{1-4}$ -alkyl, O- $C_{1-4}$ -alkyl, O-benzyl,  $CHF_2$ ,  $CF_3$ , Cl, F or  $OR^{8''''}$  and

15  $R^{6''''}$  is H, OH, O- $C_{1-4}$ -alkyl, O-benzyl,  $CF_3$ , Cl, F or  $OR^{8''''}$ ,

with the proviso that two of the radicals  $R^{4''''}$ ,  $R^{5''''}$  or  $R^{6''''}$  are H, or

20  $R^{4''''}$  and  $R^{5''''}$  together are  $-CH=C(R^{9''''})-O-$  or  $-CH=C(R^{9''''})-S-$ , with the proviso that  $R^{6''''}$  is H, or

$R^{5''''}$  and  $R^{6''''}$  together are  $-CH=CH-C(OR^{10''''})=CH-$ , with the proviso that  $R^{4''''}$  is H, and

25  $R^{7''''}$  is  $C_{1-4}$ -alkyl,  $CF_3$ , Cl or F.

Particularly preferred are salt-forming compounds of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV, in which  $R^{1''''}$  is  $CH_3$  or  $C_3H_7$  and  $R^{2''''}$  is H,  $CH_3$  or  $CH_2CH_3$ , or  $R^{1''''}$  and  $R^{2''''}$  together are  $-(CH_2)_{2-3}-$  or  $-(CH_2)_2-CHR^{7''''}$ ,

35  $R^{3''''}$  is H,  $CH_3$  or  $CH_2CH_3$ ,

$R^{4''''}$  is H or OH,  $R^{5''''}$  is H, OH,  $OCH_3$ ,  $CHF_2$  or  $OR^{8''''}$  and  $R^{6''''}$  is H, OH or  $CF_3$ , with the proviso that two of the radicals  $R^{4''''}$ ,  $R^{5''''}$  or  $R^{6''''}$  are H, or

$R^{4''''}$  and  $R^{5''''}$  together are  $-\text{CH}=\text{C}(\text{CH}_3)-\text{S}-$ , with the proviso that  $R^{6''''}$  is H, or

$R^{5''''}$  and  $R^{6''''}$  together are  $-\text{CH}=\text{CH}-\text{C}(\text{OH})=\text{CH}-$ , with the  
5 proviso that  $R^{4''''}$  is H, and

$R^{8''''}$  is  $\text{CO}-\text{C}_6\text{H}_4-\text{R}^{11''''}$  where  $\text{R}^{11''''}$  is  $\text{OC}(\text{O})-\text{C}_{1-3}\text{-alkyl}$  in the ortho-position.

10 Very particularly preferred are salt-forming compounds of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV, in which

$R^{1''''}$  is  $\text{CH}_3$  and  $R^{2''''}$  is H or  $\text{CH}_3$  or  $R^{1''''}$  and  $R^{2''''}$  together  
15 are  $-(\text{CH}_2)_{2-3}-$  or  $-(\text{CH}_2)_2-\text{CH}(\text{CH}_3)-$ ,

$R^{3''''}$  is H or  $\text{CH}_3$ ,

$R^{4''''}$  is H,  $R^{5''''}$  is OH or  $\text{OR}^{8''''}$ ,  $R^{6''''}$  is H, and  $R^{8''''}$  is  $\text{CO}-$   
20  $\text{C}_6\text{H}_4-\text{R}^{11''''}$  where  $\text{R}^{11''''}$  is  $\text{OC}(\text{O})-\text{CH}_3$  in the ortho-position.

Most preferred is the salt-forming compound of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV trans-(-)-(1R)-3-[1-(2-  
25 dimethylamino-1-methylethyl)propenyl]phenol.

The preparation of the salt-forming compounds of dimethyl-(3-arylbut-3-enyl)amine compounds of the general formula IV and, if appropriate, the separation  
30 into the optically pure antipodes can be carried out according to customary methods known to the person skilled in the art. Preferably, the preparation and, if appropriate, the separation of these compounds are carried out as described in EP 0 799 819 A1. The  
35 corresponding literature description is hereby inserted as reference and is thus regarded as part of the disclosure.

As salt-forming antiobesity agents, the pharmaceutical salt according to the invention can preferably contain D-norpseudoephedrine, phenylpropanolamine, amfepramone, mefenorex or ephedrine.

5

As salt-forming analeptics and/or antihypoxemics, the pharmaceutical salt according to the invention can preferably contain norfenefrine, heptaminol or amezinium, particularly preferably amezinium.

10

As salt-forming opioid antagonists, the pharmaceutical salt according to the invention can preferably contain levallorphan, naloxone or naltrexone.

15

As a salt-forming anthelmintic, the pharmaceutical salt according to the invention can preferably contain pyrvinium.

20

As salt-forming antiallergics, the pharmaceutical salt according to the invention can preferably contain reproterol, triprolidine, hydroxyzine, azelastine, diphenhydramine, promethazine, pheniramine, dexchlorpheniramine, clemastine, tramazoline, brompheniramine, dimetindene, levocabastine, doxylamine, cyproheptadine, carbinoxamine, meclozine, bamipine, chlorphenoxamine, ketotifen or cetirizine, particularly preferably diphenhydramine.

25

30

As salt-forming antiarrhythmics, the pharmaceutical salt according to the invention can preferably contain orciprenaline, aprindine, verapamil, metoprolol, quinidine, amiodarone, sotalol, propafenone, diltiazem, disopyramide, propranolol, ipatropium [sic], mexiletine, prajmaline, procainamide, gallopamil, propafenone, detajmium, flecainide, oxprenolol or tocainide, particularly preferably verapamil or diltiazem.

35

As salt-forming antibiotics, the pharmaceutical salt according to the invention can preferably contain vancomycin, tetracycline, clindamycin, minocycline, lincomycin, bacampicillin, ampicillin, chlortetracycline, 5 neomycin, tobramycin, netilmicin, quinine, chloroquine, ciprofloxacin, clindamycin, colistine, erythromycin, gentamicin, tobramycin [sic], cefetametpivitol, amantadine, halofantrine, saquinavir, mefloquine, framycetin, cefepime, bromhexine, cefpodoximeproxetil, 10 oxytetracycline, proguanil, pefloxacin, polymyxin B, hydroxychloroquine, spectinomycin, sultamicillin, valaciclovir or grepafloxacin.

As salt-forming antidementive (nootropics), the 15 pharmaceutical salt according to the invention can preferably contain butalamine, memantine, pyritinol, donepezil, moxaverine, meclofenoxate, dihydroergotoxin, viquidil, naftidrofuryl, dihydroergocornine, dihydroergocristine, benzoclan, procaine, deamol, 20 diisopropylamine or 3-pyridylmethanol.

As a salt-forming antidiabetic, the pharmaceutical salt according to the invention can preferably contain metformin.

25 As salt-forming antiemetics and/or antivertiginous agents, the pharmaceutical salt according to the invention can preferably contain betahistidine, dolasetrone, meclozine, hydroxycine, diphenhydramine, 30 pyridoxine, granisetron, trifluoromazine, triethylperazine, betahistine, alizapride or odansetron, particularly preferably diphenhydramine.

As a salt-forming antiepileptic, the pharmaceutical 35 salt according to the invention can preferably contain tiagabine.

As salt-forming antihypertensives, the pharmaceutical salt according to the invention can preferably contain

dihydralazine, prazosine, amiloride, bunazosine,  
nicardipine, alprenolol, candesartancilexetil,  
metoprolol, verapamil, propranolol, penbutolol,  
doxazosine, clonidine, benazepril, phenoxybenzamine,  
5 diltiazem, diisopropylamine, urapide, carteolol,  
guanethidine, guanfacine, terazosine, oxprenolol,  
cicletanine, betaxolol, nebivolol, acebutolol,  
enalapril or indoramine, particularly preferably  
verapamil or diltiazem.

10

As salt-forming antihypotensives, the pharmaceutical  
salt according to the invention can preferably contain  
etilefrine, pholedrine, norfenefrine, cafedrine,  
theodrenaline, oxilofrine, dobutamine, dopamine,  
15 phenylephrine, midodrine, heptaminol, oxedrine  
tartrate, pholedrine or gepefrine, particularly  
preferably phenylephrine.

As salt-forming antimycotics, the pharmaceutical salt  
20 according to the invention can preferably contain  
benzalkonium, econazole, miconazole, methyl-  
rosanilinium, terbinafine, amorolfine, fenticonazole,  
dequalinium, oxyconazole, croconazole, isoconazole or  
sertaconazole.

25

As a salt-forming antiinflammatory, the pharmaceutical  
salt according to the invention can preferably contain  
orphenadrine.

30 As salt-forming antitussives and/or expectorants, the  
pharmaceutical salt according to the invention can  
preferably contain ambroxole, doxycycline, bromhexine,  
dextromethorphan, diphenhydramine, terbutaline,  
chlorphenamine, eprazinone, ephedrine, chlorbutinol,  
35 pentoxyverine, pipazetate or benproperine, particularly  
preferably diphenhydramine.

As a salt-forming antisclerosis agent, the pharmaceutical salt according to the invention can preferably contain butalamine.

- 5 As  $\beta$ -receptor blockers and/or calcium channel blockers, the pharmaceutical salt according to the invention can preferably contain acebutolol, nicardipine, alprenolol, metoprolol, verapamil, enalapril, bupranolol, penbutolol, propranolol, bisoprolol, esmolol,  
10 celiprolol, benazepril, diltiazem, mepindolol, sotalol, carteolol, gallopamil or oxprenolol, particularly preferably verapamil or diltiazem.

- As salt-forming broncholytics and/or antiasthmatics,  
15 the pharmaceutical salt according to the invention can preferably contain ketotifen, reproterol, orciprenaline, salbutamol, terbutaline, ephedrine, tulobuterol, ipatropium [sic], fenoterol, terbutaline [sic], formoterol, salbutamol [sic], oxytropium or  
20 pirbuterol.

- As salt-forming cholinergics, the pharmaceutical salt according to the invention can preferably contain pyridostigmine, betanecol or neostigmine..  
25

As salt-forming diuretics, the pharmaceutical salt according to the invention can preferably contain amiloride or oxprenolol.

- 30 As salt-forming, circulation-promoting agents, the pharmaceutical salt according to the invention can preferably contain butalamine, naftidrofuryl, buflomedil, moxaverine, bencyclan or meclofenoxate.

- 35 As a salt-forming weaning agent, the pharmaceutical salt according to the invention can preferably contain naltrexone, methadone, buprenorphine.

As salt-forming geriatrics, the pharmaceutical salt according to the invention can preferably contain procaine or deanolace.

5 As salt-forming hypnotics and/or sedatives, the pharmaceutical salt according to the invention can preferably contain promethazine, zolpidem tartrate, midazolam, melperone or flurazepam.

10 As a salt-forming immunomodulator, the pharmaceutical salt according to the invention can preferably contain levamisole.

As salt-forming oral and/or pharyngeal therapeutics,  
15 the pharmaceutical salt according to the invention can preferably contain chlorhexidine or cetylpyridinium.

As a salt-forming coronary agent, the pharmaceutical salt according to the invention can preferably contain  
20 oxyfedrine.

As a salt-forming hypolipidemic, the pharmaceutical salt according to the invention can preferably contain colestipol.

25 As salt-forming local anesthetics and/or neural therapeutics, the pharmaceutical salt according to the invention can preferably contain bupivacaine, lidocaine, mepivacaine, ropivacaine, procaine,  
30 artiacaine or prilocaine.

As salt-forming gastric and/or intestinal agents, the pharmaceutical salt according to the invention can preferably contain pizotifen, pirenzepine, roxatidine,  
35 ranitidine, butinoline, methanthelinium or metoclopramide.

As salt-forming migraine agents, the pharmaceutical salt according to the invention can preferably contain

lisuride, methysergide, dihydroergotamine, ergotamine, sumatriptan, rizatriptan or naratriptan.

As salt-forming muscle relaxants, the pharmaceutical  
5 salt according to the invention can preferably contain alcuronium, mivacurium, atracurium, vecurium, pancurium, suxamethonium, tolperisone, pridinol, orphenadrine or tizamidine.

10 As a salt-forming anesthetic, the pharmaceutical salt according to the invention can preferably contain ketamine or midazolam.

As a salt-forming neuropathy preparation, the  
15 pharmaceutical salt according to the invention can preferably contain thiamine.

As salt-forming ophthalmologicals and/or otologicals, the pharmaceutical salt according to the invention can  
20 preferably contain oxybuprocaine, proxymetacaine, kanamycin, tolazoline, tetryzoline, tramazoline, phenylephrine, xylomethazoli [sic], naphazoline, timolol, metipranolol, betaxolol, befunolol, levobunolol, brimonidine, clonidine, pilocarpine,  
25 dipivefrine, aceclidine, apraclonidine, neostigmine, dorzolamide, atropine, scopolamine, cyclopentolate or homatropine, particularly preferably phenylephrine.

As salt-forming Parkinson agents, the pharmaceutical  
30 salt according to the invention can preferably contain amantadine, biperidene, selegiline, bromocriptine, trihexyphenidyl, metrixene, benzaseride, lisuride, benzatropine, ropinirol, pergolide, bupidine, procyclidine, pramipexol, bomapine or tiapride.

35 As salt-forming psychopharmaceutical agents, the pharmaceutical salt according to the invention can preferably contain tranylcypromine, amitriptyline, doxepine, maprotiline, clomipramine, opipramol,



imipramine, trimipramine, lofepramine, desipramine,  
dibenzepine, nortriptyline, mianserine, citalopram,  
fluvoxamine, fluoxetine, trazodone, paroxetine,  
nefazodone, sertraline, viloxacin, venlafaxine,  
5 promethazine, chlorprothixene, zuclopenthixol,  
pipamperone, fluphenazine, flupentixol, melperone,  
prothipendyl, thioridazine, levomepromazine,  
quetiapine, triflupromazine, perazine, fenetylline,  
methylphenidate, hydroxycine, buspirone, deanolace or  
10 memantine.

As salt-forming rhinologicals/sinusitis agents, the  
pharmaceutical salt according to the invention can  
preferably contain diphenylpyraline, xylometazoline,  
15 oxymetazoline, tramazoline, indanazoline, naphazoline  
or tetrazyline.

As salt-forming spasmolytics, the pharmaceutical salt  
according to the invention can preferably contain  
20 atropine, phenamazide, butylscopolaminium, propiverine,  
mebeverine, pipenzolate, oxybutynine, flavoxate,  
trospium, denaverine or glycopyrronium.

As salt-forming platelet aggregation inhibitors, the  
25 pharmaceutical salt according to the invention can  
preferably contain tirofiban, ticlopidine or  
clopidogrel.

As a salt-forming tuberculosis agent, the  
30 pharmaceutical salt according to the invention can  
preferably contain ethambutol.

As salt-forming urologicals, the pharmaceutical salt  
according to the invention can preferably contain  
35 choline, tolterodine, phenoxybenzamine, atropine,  
propiverine, distigmine, emepronium, tamsulosine,  
doxazosine, terazosine, alfuzosine, bamethane,  
yohimbine or sildenafil.

As salt-forming cytostatics, the pharmaceutical salt according to the invention can preferably contain aclarubicin, nimustatin, doxorubicin, bleomycin, vinblastine, vincristine, daunorubicin, decarbazine, vindesine, epirubicin, gemcitabine, procarbazon, mitoxantrone, bedamustine, idarubicin, aclarubicin [sic], irinotecan, topotecan, toremifen or tamoxifen.

The pharmaceutical salts according to the invention can be prepared according to customary methods known to the person skilled in the art. Preferably, for the preparation of the pharmaceutical salts according to the invention, at least one salt of the respective active compound and at least one salt of the respective sugar substitute are in each case dissolved separately from one another in an amount of a solvent or solvent mixture which is as small as possible, optionally with warming.

Both solutions are then combined, optionally mixed and optionally cooled. If the pharmaceutical salt according to the invention of the active compound and the sugar substitute precipitates at least partially from the optionally cooled solution, this is separated off according to customary methods, preferably by suction filtration. The pharmaceutical salt separated off is then purified, if necessary, according to customary methods known to the person skilled in the art, for example by recrystallization, washing or by stirring in a suitable solvent.

If the pharmaceutical salt has still not completely precipitated, the remaining solution is preferably concentrated completely on a rotary evaporator and the pharmaceutical salt according to the invention is extracted from the residue according to customary methods known to the person skilled in the art and purified as described above.

The solvent or solvent mixture suitable in each case for the preparation and the suitable reaction conditions, such as, for example, temperature or reaction time, can be determined by the person skilled  
5 in the art with the aid of simple preliminary tests. If both the active compound salt and the salt of the sugar substitute have an adequate solubility in water, the solvent used is preferably water. The salt of the respective active compound employed is preferably its  
10 hydrochloride, hydrobromide, phosphate, hydrogen-phosphate, hydrogensulfate, sulfate, nitrate or metilsulfate. The salt of the respective sugar substitute employed is preferably its sodium, potassium, calcium or ammonium salt.

15 Of course, it is also possible to react the respective active compound per se with [sic] the free acid of a sugar substitute with one another in a suitable reaction medium and to isolate and, if appropriate, to  
20 purify the pharmaceutical salt thus obtained according to customary methods known to the person skilled in the art.

A further subject of the present invention are  
25 medicaments comprising at least one pharmaceutical salt according to the invention and, if appropriate, physiologically tolerable excipients. The corresponding medicaments can be used for the treatment of the indications known for the respective active compounds.

30 Preferably, medicaments according to the invention which contain at least one pharmaceutical salt according to the invention of a salt-forming opioid, opioid analog, ephedrine, chloroquine, lidocaine,  
35 ethaverine, preglumetacin or triflupromazine or a salt-forming compound of the general formula I, II, III or IV indicated above and a sugar substitute are employed for the control of pain. Preferably, the medicaments according to the invention contain the

corresponding saccharinates as pharmaceutical salts of these active compounds.

For the treatment of urinary incontinence, medicaments  
5 according to the invention are preferably employed  
which contain at least one pharmaceutical salt of a  
salt-forming compound of the general formula I, II, III  
or IV indicated above, or a compound from the group  
consisting of oxybutymine, tolterodine, propiverine and  
10 trospium and a sugar substitute. Preferably, the  
medicaments according to the invention contain the  
corresponding saccharinates as pharmaceutical salts of  
these active compounds.

15 The medicaments according to the invention can be  
present in solid, semisolid or liquid form. Preferably,  
the medicaments according to the invention are suitable  
for oral administration.

20 In a preferred embodiment, the medicament according to  
the invention is present: formulated as a gel, chewing  
gum, juice, spray, tablet, chewable tablet, coated  
tablet, powder, if appropriate filled into capsules,  
easily reconstitutable dry preparations, preferably as  
25 a gel, as an aqueous or oily juice, as a sublingual  
spray, tablets or chewable tablets.

Likewise preferably, the medicament according to the  
invention can also be present formulated in  
30 multiparticulate form, preferably in the form of micro-  
tablets, microcapsules, granules, active compound  
crystals or pellets, particularly preferably in the  
form of microtablets, granules or pellets, optionally  
filled into capsules or compressed to give tablets.

35

If the medicament according to the invention is present  
in the form of granules or pellets, these can  
preferably have a size in the range from 0.1 to 3 mm,  
particularly preferably in the range from 0.5 to 2 mm.

If the medicament according to the invention is present in the form of microtablets, these can preferably have a diameter in the range from 0.5 to 5 mm, particularly preferably in the range from 1 to 3 mm and very particularly preferably in the range from 1 to 2 mm.

If the medicament according to the invention is present in the form of active compound crystals, micro- particles, micropellets or microcapsules, these can preferably have a diameter in the range from 10  $\mu$ m to 1 mm, particularly preferably in the range from 15  $\mu$ m to 0.5 mm and very particularly preferably in the range from 30  $\mu$ m to 200  $\mu$ m.

Depending on embodiment, the medicaments according to the invention can moreover contain the customary physiologically tolerable excipients known to the person skilled in the art as further constituents.

If the medicaments according to the invention are present in the form of tablets or microtablets, these can be present as physiologically tolerable excipients, preferably microcrystalline cellulose, cellulose ethers, lactose, starch, starch derivatives, sugar alcohols, calcium hydrogenphosphate and the customary binders, flow regulators, lubricants and/or disintegrants known to the person skilled in the art.

If the medicaments according to the invention are present in the form of gels or chewing gums, these can preferably contain methylparaben, propylparaben, xylitol and/or xanthan gum as physiologically tolerable excipients.

If the medicaments according to the invention are present in the form of pellets, granules or micropellets, these can preferably contain microcrystalline cellulose, cellulose ethers, lactose, starch and starch

derivatives, sugar alcohols, calcium hydrogenphosphate, fatty alcohols, esters of glycerol or fatty acid esters as physiologically tolerable excipients.

5 If the medicaments according to the invention are present in the form of microcapsules or microparticles, these can contain, depending on the nature of the process employed for their preparation, the customary physiologically tolerable excipients known to the  
10 person skilled in the art.

The medicaments according to the invention can be prepared by customary methods known to the person skilled in the art.

15 If the medicaments according to the invention are present in the form of tablets, preferably the pharmaceutical salt according to the invention and, if appropriate, the physiologically tolerable excipients  
20 are preferably mixed homogeneously with one another, processed to give granules by means of moist, dry or melt granulation and compressed to give tablets or produced by direct tableting of the pharmaceutical salt with further excipients. In addition, the tablets can  
25 preferably be produced by compression of optionally coated pellets, active compound crystals, microparticles or microcapsules.

The medicaments according to the invention in the form  
30 of pellets can preferably be produced by mixing the pharmaceutical salt and physiologically tolerable excipients, extrusion and spheronization, by build-up pelletization or by direct pelletization in a high-speed mixer or in the rotor fluidized bed. The pellets  
35 are particularly preferably prepared by extrusion of moist masses and subsequent spheronization.

Microcapsules are prepared according to customary microencapsulation processes, such as, for example, by spray drying, spray solidification or coacervation.

- 5 The medicaments according to the invention in semisolid form, such as, for example, gels or chewing gums, are preferably suitable for the administration of the pharmaceutical salt according to the invention via the oral mucosa, the medicaments according to the invention
- 10 in solid or liquid form, such as, for example, oily or aqueous juices, tablets or multiparticulate forms are preferably suitable for the administration of the pharmaceutical salt according to the invention via the gastric tract. If the absorption of active compound
- 15 from the medicament according to the invention in solid form is only intended via the gastric tract, they must have at least one enteric coating. This enteric coating enables them to pass through the gastric tract undissolved and the pharmaceutical salt is only
- 20 released in the intestinal tract. Preferably, the enteric coating dissolves at a pH of between 5 and 7.5.

The medicament according to the invention can contain the pharmaceutical salt according to the invention also

25 partially or completely in delayed-release form.

The delaying of the release of active compound is preferably based on the application of a release-delaying coating, on embedding in a release-delaying

30 matrix, binding to an ion-exchange resin or on a combination of these abovementioned release-delaying methods.

Preferably, the release-delaying coating is based on a

35 water-insoluble, optionally modified natural or synthetic polymer or on a natural, semisynthetic or synthetic wax or fat or fatty alcohol or a mixture of at least two of these abovementioned components.

Water-insoluble polymers employed for the preparation of a release-delaying coating are preferably poly-(meth)acrylates, particularly preferably poly(C<sub>1-4</sub>) alkyl (meth)acrylates, poly(C<sub>1-4</sub>)dialkylamino-(C<sub>1-4</sub>)-  
5 alkyl (meth)acrylates and/or their copolymers, very particularly preferably ethyl acrylate/methyl methacrylate copolymers having a molar ratio of the monomers of 2:1, ethyl acrylate/methyl methacrylate/trimethylammonium ethyl methacrylate  
10 chloride copolymers having a molar ratio of the monomers of 1:2:0.1, ethyl acrylate/methyl methacrylate/trimethylammonium ethyl methacrylate chloride copolymers having a molar ratio of the monomers of 1:2:0.2 or a mixture of at least two of  
15 these abovementioned polymers as a coating material.

These coating materials are obtainable on the market as 30% strength by weight aqueous latex dispersions under the names Eudragit RS30D®, Eudragit NE30D® and Eudragit  
20 RL30D® and are preferably also employed as a coating material as such.

Likewise preferably, the water-insoluble polymers employed for the preparation of the release-delaying  
25 coating for the medicaments according to the invention can be polyvinyl acetates, optionally in combination with further excipients. These are obtainable on the market as an aqueous dispersion containing 27% by weight of polyvinyl acetate, 2.5% by weight of povidone  
30 and 0.3% by weight of sodium lauryl sulphate (Kollicoat SR 30 D®).

In a further preferred embodiment, the release-delaying coatings of the medicaments according to the invention  
35 are based on water-insoluble cellulose derivatives, preferably alkylcelluloses, such as, for example, ethylcellulose, or on cellulose esters, such as, for example, cellulose acetate, as a coating material. The coatings of ethylcellulose or cellulose acetate are



preferably applied from aqueous pseudolatex dispersion. Aqueous ethylcellulose-pseudolatex dispersions are stocked on the market as 30% strength by weight dispersions (Aquacoat®) or as 25% strength by weight  
5 dispersions (Surelease®) and as such are preferably also employed as a coating material.

As natural, semisynthetic or synthetic waxes, fats or fatty alcohols, the release-delaying coating in the  
10 medicament according to the invention can preferably contain carnauba wax, beeswax, glycerol monostearate, glycerol monobehenate (Compritol ATO888®), glycerol ditripalmitostearate (Precirol AT05®), microcrystalline wax, cetyl alcohol, cetylstearyl alcohol, or a mixture  
15 of at least two of these components.

If the release-delaying coating is based on a water-insoluble, optionally modified natural and/or synthetic polymer, the coating dispersion or solution can  
20 contain, in addition to the corresponding polymer, a customary physiologically tolerable plasticizer known to the person skilled in the art in order to lower the minimum film temperature necessary.

25 Suitable plasticizers are, for example, lipophilic diesters of an aliphatic or aromatic dicarboxylic acid of C<sub>6</sub>-C<sub>40</sub> and an aliphatic alcohol of C<sub>1</sub>-C<sub>8</sub>, such as, for example, dibutyl phthalate, diethyl phthalate, dibutyl sebacate or diethyl sebacate, hydrophilic or lipophilic  
30 esters of citric acid, such as, for example, triethyl citrate, tributyl citrate, acetyltributyl citrate or acetyltriethyl citrate, polyalkylene glycols, such as, for example, polyethylene glycols or propylene glycols, esters of glycerol, such as, for example, triacetin,  
35 Myvacet® (acetylated mono- and diglycerides, C<sub>23</sub>H<sub>44</sub>O<sub>5</sub> to C<sub>25</sub>H<sub>47</sub>O<sub>7</sub>), medium-chain triglycerides (Miglyol®), oleic acid or mixtures of at least two of the abovementioned plasticizers.

Preferably, aqueous dispersions of Eudragit RS® and optionally Eudragit RL® contain triethyl citrate as a plasticizer.

- 5 Preferably, the release-delaying coating contains the plasticizer(s) in amounts of 5 to 50% by weight, particularly preferably 10 to 40% by weight and very particularly preferably 10 to 30% by weight, based on the amount of the polymer employed.

10

In individual cases, for example for cellulose acetate, higher amounts of plasticizers, preferably up to 110% by weight, based on the amount of cellulose acetate, can also be employed.

15

- In addition, the release-delaying coating can contain further customary excipients known to the person skilled in the art, such as, for example, lubricants, preferably talc or glycerol monostearate, color  
20 pigments, preferably iron oxides or titanium dioxide, or surfactants, such as, for example, Tween 80®.

- The release profile of the delayed active compound component can be adjusted by the customary methods  
25 known to the person skilled in the art, such as, for example, by the thickness of the coating or by the use of further excipients as constituents of the coating. Suitable excipients are, for example, hydrophilic or pH-dependent pore-forming agents, such as, for example,  
30 sodium carboxymethylcellulose, cellulose acetate phthalate, hydroxypropylmethylcellulose acetate succinate, lactose, polyethylene glycol or mannitol or water-soluble polymers, such as, for example, polyvinylpyrrolidone or water-soluble celluloses,  
35 preferably hydroxypropylmethylcellulose or hydroxypropylcellulose.

The release-delaying coating can also contain insoluble or lipophilic excipients, such as, for example, alkylized silicone, which is stocked on the market, for

example, as Aerosil R972<sup>®</sup>, or magnesium stearate for the further intensification of the delaying.

5 The respective formulation of the medicament according to the invention can optionally also contain, in addition to the release-delaying coating, at least one further coating. This can be, for example, a coating for improving the taste or an enteric coating.

10 The enteric coating is preferably based on methacrylic acid/methyl methacrylate copolymers having a molar ratio of the respective monomers of 1:1 (Eudragit L<sup>®</sup>), methacrylic acid/methyl methacrylate copolymers having a molar ratio of the respective monomers of 1:2  
15 (Eudragit S<sup>®</sup>), methacrylic acid/ethyl acrylate copolymers having a molar ratio of the respective monomers of 1:1 (Eudragit L30D-55<sup>®</sup>), methacrylic acid/methyl acrylate/methyl methacrylate copolymers having a molar ratio of the respective monomers of  
20 7:3:1 (Eudragit FS<sup>®</sup>), shellac hydroxypropylmethylcellulose acetate succinate, cellulose acetate phthalate or a mixture of at least two of these abovementioned components, which can optionally also be employed in combination with the abovementioned water-  
25 insoluble poly(meth)acrylates, preferably in combination with Eudragit NE30D<sup>®</sup> and/or Eudragit RL<sup>®</sup> and/or Eudragit RS<sup>®</sup>.

30 The coatings can be applied by customary processes suitable for the respective coating and known to the person skilled in the art, such as, for example, by spraying on solutions, dispersions or suspensions, by melt processes or by powder application processes. The solutions, dispersions or suspensions can be employed  
35 in the form of aqueous and/or organic solutions or dispersions. In this context, aqueous dispersions are preferably employed. Organic solvents which can preferably be used are alcohols, for example ethanol or isopropanol, ketones, such as, for example, acetone,

esters, for example ethyl acetate, chlorinated hydrocarbons, such as, for example, dichloromethane, with alcohols or ketones being particularly preferably employed. It is also possible to employ mixtures of at least two of the abovementioned solvents.

If the medicament is present in multiparticulate form and the active compound is to be released at least partially in delayed form, the release-delaying coating is preferably applied such that the multiparticulate forms comprising the active compound salt are coated after their preparation with the corresponding polymers and, if appropriate, another active compound and/or the same active compound salt and, if appropriate, further physiologically tolerable excipients from aqueous and/or organic media, preferably from aqueous media, with the aid of the fluidized bed process and the coating is preferably simultaneously dried in the fluidized bed at customary temperatures and, if appropriate, annealed if necessary.

Preferably, the drying of the coating is carried out for poly(meth)acrylate coatings at a feed air temperature in the range from 30 to 50°, particularly preferably in the range from 35 to 45°C.

For coatings based on cellulose, such as, for example, ethylcellulose or cellulose acetate, the drying is preferably carried out at a temperature in the range from 50 to 80°C, particularly preferably in the range from 55 to 65°C.

Wax coatings can be applied by melt coating in the fluidized bed and cooled at temperatures below the respective melt range after the coating for complete solidification. The application of wax coatings can also be carried out by spraying on their solutions in organic solvents.

For the modification of the active compound release profile, the medicament according to the invention can contain the pharmaceutical salt whose release is to be delayed also in a release-delaying matrix, preferably  
5 uniformly dispersed.

Matrix materials which can be used are physiologically tolerable, hydrophilic materials which are known to the person skilled in the art. Preferably, the hydrophilic  
10 matrix materials used are polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins. Very particularly preferably, the matrix materials employed are ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxy-  
15 methylcellulose, poly(meth)acrylic acid and/or their derivatives, such as, for example, their salts, amides or esters.

Likewise preferred are matrix materials made of  
20 hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or appropriate esters or ethers or mixtures of at least two of the abovementioned materials. Particularly preferably, the hydrophobic materials employed are  
25 mono- or diglycerides of  $C_{12}$ - $C_{30}$ -fatty acids and/or  $C_{12}$ - $C_{30}$ -fatty alcohols and/or waxes or mixtures of at least two of the abovementioned materials.

It is also possible to employ mixtures of the above-  
30 mentioned hydrophilic and hydrophobic materials as a release-delaying matrix material.

The release-delaying matrix can be prepared by the customary methods known to the person skilled in the  
35 art.

A further subject of the invention is also the use of at least one pharmaceutical salt according to the invention and, if appropriate, physiologically

tolerable excipients for the production of a medicament. The corresponding medicaments can be used for the treatment of the indications known for the respective active compounds.

5

Preferred is the use of at least one pharmaceutical salt of a salt-forming opioid, opioid analog, ephedrine, chloroquine, lidocaine, ethaverine, preglumetacin, truflupromazine or a salt-forming  
10 compound of the general formula I, II, III or IV indicated above for the production of a medicament for the control of pain, the salts of these active compounds used preferably being their saccharinates.

15 Likewise preferred is the use of at least one pharmaceutical salt of a salt-forming compound of the general formula I, II, III or IV indicated above for the production of a medicament for the treatment of urinary incontinence, the salts of these active  
20 compounds used preferably being their saccharinates.

The total amount of the respective pharmaceutical salt to be administered to the patient varies, for example, depending on the the weight of the patient, on the  
25 indication and the degree of severity of the pain or of the disorder. It is known to the person skilled in the art on account of the properties of the respective active compounds in what doses these are to be administered in order to achieve the desired effect.

30

The pharmaceutical salts according to the invention of a pharmaceutical active compound and a sugar substitute are distinguished compared with the conventionally used salts of these active compounds customarily by a lower  
35 solubility in water. Preferably, these are the saccharinates of the respective active compounds, whose water solubility is usually  $\leq 250$  mg/ml and, compared with the water solubility of the conventional salts of

the corresponding active compound, is usually lowered by at least 50%.

By this means, the formulation of these pharmaceutical salts to give medicaments, for example the preparation of granules by extrusion, is also simplified. On account of the altered solubility, the pharmaceutical salts according to the invention further enable more effective release-delaying of the active compound using customary delaying processes in comparison to salts customarily used. Delayed-release medicaments which contain these pharmaceutical salts according to the invention can therefore be produced more simply and more inexpensively. This also applies for other modifications of the medicaments according to the invention, such as, for example, with enteric coatings.

From the medicaments according to the invention, which are employed for the administration of the respective pharmaceutical salt via the oral mucosa or the gastric tract, a largely controlled release of the respective active compound without the use of a release-delaying matrix and/or a release-delaying coating, but if appropriate with an enteric coating, is moreover achieved.

The medicaments according to the invention in the form to be administered orally, which release the respective active compound as early as on or immediately after administration, furthermore have the advantage that their strongly bitter or nauseating taste is compensated by the simultaneous release of the sugar substitute. The adherence to the dosage instructions in the patients thereby improves and the medicaments which contain the respective active compound as a salt experience a greater acceptance. The medicaments according to the invention are moreover also suitable for diabetics.

For a large number of the abovementioned active compounds, the water solubility of the conventional active compound salts is known, for example from Pharmazeutische Stoffliste [Pharmaceutical Substance  
5 List], 12th edition ABDA Pharma-Daten-Service, 65735 Eschborn/Taunus. The corresponding disclosure [sic] is hereby inserted as reference and is thus regarded as part of the disclosure.

10 If the water solubility of an active compound salt is not known, it can be determined according to the method indicated below, according to which the water solubility of the pharmaceutical salts according to the invention has also been determined:

15 In a clear colorless vessel made of transparent material, such as, for example, glass or plastic, 1 ml of ion-free water or a fraction (amount A in ml) thereof is introduced at a temperature of 20°C. While  
20 stirring with a magnetic stirrer rod, the conventional active compound salt to be tested or the pharmaceutical salt according to the invention was then added in portions.

25 If the amount of salt B added (in mg) completely dissolved, further amounts of the respective salt were slowly added. Each further addition was recorded and the solution behavior observed. As soon as the first turbidity due to undissolved salt was found by  
30 observation against a suitable background, stirring was continued for a further 10 minutes. If undissolved constituents subsequently remained, the sum C (in mg) of the amount of substance employed was determined. If a clear solution resulted again on stirring, further  
35 small amounts of the respective salt were added and the mixture was in each case stirred again for 10 minutes until a first turbidity remained on account of undissolved salts. The excess amount of undissolved substance was then brought into solution with stirring



by addition of small amounts of water. After a clear solution had been obtained, the sum D (in ml) of the amount of water employed was determined. The solubility of the respective salt per 1 ml of water was then  
5 calculated according to the following formula:

$$\begin{array}{l} \text{Water solubility of the active compound salt} \\ \text{in mg/ml of water} = \frac{(C/A) + (C/D)}{2} \end{array}$$

10

If the amount B added (in mg) of the respective salt did not dissolve immediately and a turbidity resulted, after the addition of the salt the mixture was stirred for a further 10 minutes. If undissolved salt still  
15 remained then, the undissolved portion was brought into solution by addition of small amounts of water with stirring. After obtainment of a clear solution, the sum E (in ml) of the amounts of water employed was determined. The solubility of the respective salt per  
20 1 ml of water was then calculated according to the following formula:

$$\begin{array}{l} \text{Water solubility of the active compound salt} \\ \text{in mg/ml of water} = \frac{B}{E} \end{array}$$

25

The invention is explained below with the aid of examples. These explanations are only by way of example and do not restrict the general inventive concept.  
30

**Examples:**

Example 1:

5 The preparation and the subsequent separation of the optically pure compound (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol was carried out according to DE-A-4426245. The corresponding part of the disclosure [sic] is hereby inserted as reference and is  
10 thus regarded as part of the disclosure.

For the preparation of (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol saccharinate, 2.58 g (10 mmol) of (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-  
15 methylpropyl)phenol hydrochloride and 2.42 g (10 mmol) of saccharin-sodium dihydrate were in each case completely dissolved with warming in an amount of water which was as small as possible. Both solutions were then mixed with one another with stirring and then  
20 placed in a cool place overnight. The precipitated (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol saccharinate was separated off from the supernatant mother liquor, purified with ethanol and isolated according to conventional methods.

25

Example 2:

For the preparation of diphenhydramine saccharinate, 5.0 g (17.1 mmol) of diphenhydramine hydrochloride and  
30 4.13 g (17.1 mmol) of saccharin-sodium dihydrate were in each case completely dissolved with warming in an amount of water which was as small as possible. Both solutions were then mixed with one another with stirring and then placed in a cool place overnight. The  
35 precipitated diphenhydramine saccharinate was separated off from the supernatant mother liquor, purified with ethanol and isolated according to conventional methods.

Example 3:

For the preparation of verapamil saccharinate, 415 mg (0.845 mmol) of verapamil hydrochloride and 204 mg  
5 (0.845 mmol) of saccharin-sodium dihydrate were in each case completely dissolved with warming in an amount of water which was as small as possible. Both solutions were then mixed with one another with stirring and then placed in a cool place overnight. The precipitated  
10 verapamil saccharinate was separated off from the supernatant mother liquor, purified with ethanol and isolated according to conventional methods.

Example 4:

15 For the preparation of morphine saccharinate, 285 mg (0.76 mmol) of morphine hydrochloride trihydrate and 183 mg (0.76 mmol) of saccharin-sodium dihydrate were in each case completely dissolved with warming in an amount of water which was as small as possible. Both  
20 solutions were then mixed with one another with stirring and then placed in a cool place overnight. The precipitated morphine saccharinate was separated off from the supernatant mother liquor, purified with  
25 ethanol and isolated according to conventional methods.

Example 5:

For the preparation of an oral gel, 0.33 g of  
30 methylparaben, 0.05 g of propylparaben and 75.0 g of xylitol were first dissolved in 198.0 g of purified water at a temperature of 80°C and the mixture was then cooled to 40°C. Then, initially 0.94 g of diphenhydramine saccharinate obtained according to  
35 example 2 and subsequently 2 g of xanthan gum were added with stirring, stirring was continued for one hour and evaporated water was replaced. After cooling to a temperature of 20 to 25°C, the mixture was

flavored with 0.625 g of Tutti-Frutti 9/008897 (Dragoco Gerberding & Co. AG, 37603 Holzminden) while stirring.

Example 6:

5

5 g of comminuted chewing gum mass (Popeye Amural Confections, Yorkville, Illinois, USA) were warmed to a temperature of 30 to 40°C in a Fanta dish. 187.9 mg of diphenhydramine saccharinate obtained according to  
10 example 2 were then incorporated into the viscous chewing gum mass using a pestle. The homogeneous mass was then portioned into teflonized molds to give portions of 1 g each.

15 The taste test showed that the chewing gums which contained the diphenhydramine saccharinate had an excellent taste at the start and were still enjoyable even after a relatively long chewing time.

20 Example 7:

For the preparation of a juice on an aqueous basis, 0.33 g of methylparaben, 0.05 g of propylparaben and 75.0 g of xylitol were dissolved in 199.22 g of  
25 purified water at a temperature of 80°C. The mixture was cooled to 40°C and 78.5 mg of (+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol saccharinate obtained according to example 1 were added with stirring. 0.25 g of xanthan gum was then added,  
30 stirring was continued for one hour and evaporated water was replaced. After cooling to [lacuna] temperature of 20 to 25°C, the mixture was flavored while stirring with 0.075 g of orange-mandarin flavor 10888-56 (Givaudan Roure Flavors Ltd. CH 8600  
35 Dübendorf).

Example 8:

In this example, the water solubility of certain pharmaceutical salts and of conventional salts of the corresponding active compound was determined according to the method indicated above. The solubility values thus obtained are presented in table 1 below:

**Table 1:**

Comparison of the water solubilities of certain pharmaceutical salts according to the invention and corresponding conventional salts of these active compounds. The conventional salt employed in each case is indicated in brackets.

Active compound	Solubility of the active compound salt in mg/ml of water	Solubility of the active compound saccharinate in mg/ml of water
(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol	261 (hydrochloride)	31
(1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)cyclohexane-1,3-diol [sic]	500 (hydrochloride)	71
(+)-(1S,2S)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)phenol	650 (hydrochloride)	55
(-)-(1S,2S)-3-(3-dimethylamino-1-ethyl-1-fluoro-2-methylpropyl)phenol	568 (hydrochloride)	130
(-)-(2S,3S)-1-dimethylamino-3-(3-methoxyphenyl)-	2000 (hydrochloride)	90

Active compound	Solubility of the active compound salt in mg/ml of water	Solubility of the active compound saccharinate in mg/ml of water
2-methylpentan-3-ol		
(+)-(1R,2R,4S)-2-dimethylaminomethyl-4-(4-fluorobenzyl-oxy)-1-(3-methoxy-phenyl)cyclohexanol	33 (hydrochloride)	10
Morphine	52 (hydrochloride trihydrate)	25
Amezinium	25 (metilsulfate)	8
Phenylephrine	1250 (hydrochloride)	380
Verapamil	200 (hydrochloride)	7
Diphenhydramine	1000 (hydrochloride)	7
Benzalkonium	500 (hydrochloride)	< 2
Codeine	250 (phosphate hemihydrate)	200
Hydromorphone	330 (hydrochloride)	130
Buprenorphine	14 (hydrochloride)	2

As can be seen from the solubility values according to table 1, the solubility of the respective active compound saccharinates is lowered compared with the corresponding conventional active compound salts.